REMARKS/ARGUMENTS

Claims 28-35 and 38-40 are pending in this application.

I. Claim Rejections Under 35 U.S.C. §101 and §112, First Paragraph

Claims 28-35 and 38-40 remain rejected under 35 U.S.C. § 101 allegedly "because the claimed invention is not supported by either a specific and/or substantial asserted utility or a well established utility." (Page 2 of the instant Office Action). Claims 28-35 and 38-40 further remain rejected under 35 U.S.C. §112, first paragraph, allegedly "since the claimed invention is not supported by either a specific and/or substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention." (Page 8 of the instant Office Action).

Applicants submit, as discussed below, that not only has the PTO not established a *prima facie* case for lack of utility, but that the antibodies of Claims 28-35 and 38-40 possess a specific and substantial asserted utility, and that based upon this utility, one of skill in the art would know how to use the claimed antibodies without undue experimentation.

The gene amplification data disclosed in Example 143 establishes a credible, substantial and specific patentable utility for the PRO1759 polypeptide.

First of all, Applicants respectfully maintain the position that the specification discloses at least one credible, substantial and specific asserted utility for the claimed PRO1788 polypeptide for the reasons previously set forth in Applicants' Responses filed on January 18, 2005 and July 8, 2005, in Applicants' Appeal Brief filed on January 11, 2006, in the Preliminary Amendment filed on August 11, 2006, and in the Supplemental Amendment filed on October 3, 2006.

Furthermore, as discussed in Applicants' previous Responses, Applicants rely on the gene amplification data for patentable utility of the claimed PRO1788 polypeptide. The gene amplification data for the gene encoding the PRO1788 polypeptide is clearly disclosed in the instant specification under Example 143. As previously discussed, a ΔCt value of at least 1.0 was observed for PRO1788 in at least eight of the tumors listed in Table 8. PRO1788 showed approximately 1.09-2.58 ΔCt units which corresponds to $2^{1.09}$-$2^{2.58}$ fold amplification or 2.12-

fold to 6-fold amplification in primary colon tumors (CT1, CT3, CT4, CT8, CT9, CT10, CT12 and CT14). (See Table 8 and page 506, lines 26-33 of the specification). Accordingly, the present specification clearly discloses overwhelming evidence that the gene encoding the PRO1788 polypeptide is significantly amplified in colon tumors.

The Examiner asserts that it is "imperative to find evidence in the relevant scientific art as to whether or not a small increase in DNA levels would be considered by the skilled artisan to be predictive of increases in subsequent polypeptide levels." (Page 6 of the instant Office Action).

Applicants respectfully submit that the Examiner seems to have applied a heightened utility standard in this instance, which is legally incorrect. Applicants have shown that the gene encoding PRO1788 demonstrated significant amplification, from 2.12 to 6-fold, in eight colon tumors.

In support, Applicants have submitted, in their Response filed on January 18, 2005, a Declaration by Dr. Audrey Goddard. Applicants particularly draw the Examiner's attention to page 3 of the Goddard Declaration which clearly states that:

> It is further my considered scientific opinion that an at least **2-fold increase** in gene copy number in a tumor tissue sample relative to a normal (*i.e.*, non-tumor) sample is significant and useful in that the detected increase in gene copy number in the tumor sample relative to the normal sample serves as a basis for using relative gene copy number as quantitated by the TaqMan PCR technique as a diagnostic marker for the presence or absence of tumor in a tissue sample of unknown pathology. Accordingly, a gene identified as being amplified at least 2-fold by the quantitative TaqMan PCR assay in a tumor sample relative to a normal sample is **useful as a marker for the diagnosis of cancer**, for monitoring cancer development and/or for measuring the efficacy of cancer therapy.

(Emphasis added).

By referring to the 2.12-fold to 6-fold amplification of the PRO1788 gene in colon tumors as "small," the Examiner appears to ignore the teachings within an expert's declaration without any basis, or without presenting any evidence to the contrary. Applicants respectfully draw the Examiner's attention to the Utility Examination Guidelines (Part IIB, 66 Fed. Reg. 1098 (2001)) which state that, "Office personnel must accept an opinion from a qualified expert that is based

upon relevant facts whose accuracy is not being questioned; it is improper to disregard the opinion solely because of a disagreement over the significance or meaning of the facts offered."

Thus, given the absence of any evidence to the contrary, Applicants maintain that the 2.12- to 6-fold amplification disclosed for the PRO1788 gene is significant and forms the basis for the utility claimed herein.

A *prima facie* case of lack of utility has not been established

The Examiner asserts that the gene amplification data provided in the specification cannot provide utility for the claimed PRO1788 polypeptide because "'increase in gene copy number' (*i.e.*, DNA data) is not equivalent to increased mRNA levels, which are not equivalent to increased polypeptide levels to which the claimed antibodies bind." (Page 3 of the instant Office Action). In support of this assertion, the Examiner refers to the references of record by Haynes, Hu, Chen, Pennica and Konopka.

Applicants have previously explained, in their previous Responses and Appeal Brief, the reasons why the Haynes, Hu, Chen, Pennica and Konopka papers of record do not provide sufficient reasons to doubt the statements by Applicants that PRO1788 has utility. As previously discussed, the law does not require the existence of a "necessary" correlation between mRNA and protein levels. Nor does the law require that protein levels be "accurately predicted." According to the authors themselves, the data in the above cited references confirm that there is a general trend between protein expression and transcript levels, which meets the "more likely than not standard" and show that a positive correlation exists between mRNA and protein.

The Examiner refers to the reference of record by Lewin as teaching that "control of gene expression can occur at multiple stages, and that production of mRNA cannot inevitably be equated with production of protein." (Page 6 of the instant Office Action).

Applicants respectfully submit that the utility standard is not **absolute certainty**. Rather, to overcome the presumption of truth that an assertion of utility by an applicant enjoys, the PTO must establish that it is **more likely than not** that one of ordinary skill in the art would doubt the truth of the statement of utility. Therefore, Applicants **do not need** to establish that transcription initiation is **the only means** of regulating gene expression in order to meet the utility standard.

Instead, as long as it is the most common point of regulation, as admitted by the Examiner, it would be more likely than not that a change in the transcription level of a gene gives rise to a change in translation level of a gene. Applicants note that Lewin makes clear that it is far more likely than not that protein levels for any given gene are regulated at the transcriptional level. In particular, Lewin states that "having acknowledged that control of gene expression can occur at multiple stages, and that production of RNA cannot inevitably be equated with production of protein, it is clear that the overwhelming majority of regulatory events occur at the initiation of transcription." *Genes VI* at 847-848 (Emphasis added). Thus, the utility standard is met.

The Examiner next refers to the reference of record by Futcher *et al.* as stating that "Gygi et al. feel that mRNA abundance is a poor predictor of protein abundance." (Page 7 of the instant Office Action).

Applicants respectfully point out that Futcher *et al.* refer to Gygi *et al.* in the process of explaining in detail why their results did show a correlation between mRNA and protein levels even for low abundance proteins, while the previous study by Gygi *et al.* did not. In fact, Futcher *et al.* concluded that "**several statistical methods show a strong and significant correlation between mRNA abundance and protein abundance.**" (Page 7360, col. 2; Emphasis added).

The authors note that Gygi *et al.* completed a similar study that generated broadly similar data, but reached different conclusions. Futcher *et al.* point out that "the different conclusions are also partly due to different methods of statistical analysis, and to real differences in data." Futcher *et al.* note that Gygi *et al.* used the Pearson product-moment correlation coefficient (r_p) and point out that "a calculation of r_p is inappropriate" because the mRNA and protein abundances are not normally distributed. (Page 7367, col. 1). In contrast, Futcher *et al.* used two different statistical approaches to determining the correlation between mRNA and protein abundances. First, they used the Spearman rank correlation coefficient (r_s), an nonparametric statistic that does not require the data to be normally distributed. Using the r_s, the authors found that mRNA abundance was well correlated with protein abundance ($r_s = 0.74$). Applying this statistical approach to the data of Gygi *et al.* **also** resulted in a good correlation ($r_s = 0.59$), although the correlation was not quite as strong as for the Futcher *et al.* data. In a second approach, Futcher *et al.* transformed the mRNA and protein data to forms where they were

normally distributed, in order to allow calculation of an r_p. Two types of transformation (Box-Cox and logarithmic) were used, and **both** resulted in good correlations between mRNA and protein abundance for Futcher *et al.*'s data.

Futcher *et al.* also note that the two studies used different methods of measuring protein abundance. Gygi *et al.* cut spots out of each gel and measured the radiation in each spot by scintillation counting, whereas Futcher *et al.* used phosphorimaging of intact gels coupled to image analysis. Futcher *et al.* point out that Gygi *et al.* may have systematically overestimated the amount of the lowest-abundance proteins, because of the difficulty in accurately cutting out very small spots from the gel, and because of difficulties in background subtraction for small, weak spots.

In addition, Futcher *et al.* note that they used both SAGE data and RNA hybridization data to determine mRNA abundances, which is most helpful to accurately measure the least abundant mRNAs. As a result, while the Futcher data set "maintains a good correlation between mRNA and protein abundance even at low protein abundance" (page 7367, col. 2), the Gygi data shows a strong correlation for the most abundant proteins, but a poor correlation for the least abundant proteins in their data set. Futcher *et al.* conclude that "**the poor correlation of protein to mRNA for the nonabundant proteins of Gygi *et al.* may reflect difficulty in accurately measuring these nonabundant proteins and mRNAs, rather than indicating a truly poor correlation *in vivo.***" (Page 7367, col. 2; Emphasis added). Thus, while these lowest abundant proteins do show a poor correlation, this is almost certainly due to the less accurate methods used to measure the abundance of these proteins, and **not** to any actual lack of correlation.

Applicants further note that, as Futcher *et al.* was published later than Gygi *et al.*, Futcher's conclusions should be considered as the updated view in the art, which supports the existence of a correlation between mRNA and protein levels.

It is "more likely than not" for amplified genes to have increased mRNA and protein levels

Applicants have submitted ample evidence to show that, in general, if a gene is amplified in cancer, it is more likely than not that the encoded protein will be expressed at an elevated level. First, the articles by Orntoft *et al.*, Hyman *et al.*, and Pollack *et al.*, (made of record in

Information Disclosure Statement filed on January 18, 2005) and the articles by Bea *et al.* and Godbout *et al.* (made of record in Information Disclosure Statement filed on August 11, 2006) collectively teach that in general, gene amplification increases mRNA expression.

Second, Applicants have submitted over a hundred references, along with the Declarations of Dr. Paul Polakis and Dr. Randy Scott with their Responses filed on January 18, 2005 and August 11, 2006, which collectively teach that, in general, there is a correlation between mRNA levels and polypeptide levels.

Applicants respectfully point out that the Declaration by Dr. Polakis (Polakis II) presents evidentiary data in Exhibit B. Exhibit B of the Declaration identifies 28 gene transcripts out of 31 gene transcripts (*i.e.*, greater than 90%) that showed good correlation between tumor mRNA and tumor protein levels. As Dr. Polakis' Declaration (Polakis II) says "[a]s such, in the cases where we have been able to quantitatively measure both (i) mRNA and (ii) protein levels in both (i) tumor tissue and (ii) normal tissue, we have observed that in the vast majority of cases, there is a very strong correlation between increases in mRNA expression and increases in the level of protein encoded by that mRNA."

Applicants have also submitted, with their Response filed on August 11, 2006, a Declaration by Dr. Randy Scott ("the Scott Declaration"). Dr. Scott was a co-founder of Incyte Pharmaceuticals, Inc., the world's first genomic information business, and is currently the Chairman and Chief Executive Officer of Genomic Health, Inc., a life sciences company located in Redwood City, California, which provides individualized information on the likelihood of disease recurrence and response to certain types of therapy using gene expression profiling. Based on his more than 15 years of personal experience with the DNA microarray technique and its various uses in the diagnostic and therapeutic fields, and his familiarity with the relevant art, Dr. Scott unequivocally confirms that, as a general rule, there is a good correlation between mRNA and protein levels in a particular tissue.

As stated in paragraph 8 of the Scott Declaration:

> DNA microarray analysis has been extensively used in drug development and in diagnosis of various diseases. ..... Due to its importance in drug discovery and in the field of diagnostics, microarray technology has not only become a laboratory mainstay but also created a world-wide market of over $600 million in the year of

2005. A long line of companies, including Incyte, Affymetrix, Agilent, Applied Biosystems, and Amersham Biosciences, made microarray technology a core of their business.

In paragraph 10 of his Declaration, Dr. Scott explains the reasons for the wide-spread use and impressive commercial success of this technique, stating:

> One reason for the success and wide-spread use of the DNA microarray technique, which has led to the emergence of a new industry, is that generally there is a good correlation between mRNA levels determined by microarray analysis and expression levels of the translated protein. Although there are some exceptions on an individual gene basis, **it has been a consensus in the scientific community that elevated mRNA levels are good predictors of increased abundance of the corresponding translated proteins in a particular tissue**. Therefore, diagnostic markers and drug candidates can be readily and efficiently screened and identified using this technique, without the need to directly measure individual protein expression levels. (Emphasis added).

The Declaration, which is based on Dr. Scott's unparalleled experience with both the microarray technique and its industrial and clinical applications, supports Applicants' position that the microarray technology is not only mature, reliable and well-accepted in the art, but also has been extensively used in drug development and in diagnosis of various diseases and produced enormous commercial success. Therefore, if a gene, such as the gene encoding the PRO1788 polypeptide, has been identified to be over-expressed in a certain disease, such as colon cancer, it is more likely than not that the protein product is also overexpressed in the disease.

The Examiner asserts that "this declaration does not provide any data for the Examiner to independently draw any conclusions. Only Declarant Scott's conclusions/'opinions' are provided in this declaration." (Page 4 of the instant Office Action).

Applicants respectfully submit that, to the contrary, the Scott Declaration has provided ample factual data to support Dr. Scott's conclusion. For example, Dr. Scott states at Paragraph 8 of his Declaration that "due to its importance in drug discovery and in the field of diagnostics, microarray technology has not only become a laboratory mainstay but also created a world-wide market of over $600 million in the year of 2005. A long line of companies, including Incyte, Affymetix, Agilent, Applied Biosystems, and Amersham Biosciences, made microarray technology a core of their business." (Emphasis added). These factual data strongly support

Dr. Scott's conclusion that microarray technology is not only mature, reliable and well-accepted in the art, but also has been extensively used in drug development and in diagnosis of various diseases and produced enormous commercial success. Applicants note that evidentiary support should not be construed narrowly as specific experimental data because neither the law nor the Utility Guidelines indicate such a narrow interpretation. Thus, contrary to the Examiner's assertions, Dr. Scott not only provides his opinion, but also provides evidentiary facts to support his conclusions.

The Examiner further asserts that "Scott does state that 'direct measurement of protein expression levels remain non-trivial', which is the issue directly related to this rejection." (Page 4 of the instant Office Action).

Applicants respectfully submit that the Examiner appears to be taking this statement out of context. While direct measurement of protein levels may remain "non-trivial," the issue at hand, which the Scott Declaration addresses, is that it is not necessary to carry out "direct measurements" of protein levels because, as Dr, Scott explains, "**generally there is a good correlation between mRNA levels determined by microarray analysis and expression levels of the translated protein**." Dr. Scott concludes that "[t]herefore, diagnostic markers and drug candidates can be readily and efficiently screened and identified using this technique, **without the need to directly measure individual protein expression levels.** (Emphasis added).

The Examiner further asserts that the articles of record by Orntoft *et al.*, Hyman *et al.*, Pollack *et al.*, Bea *et al.* and Godbout *et al.* do not support a general mRNA/protein correlation, and that Hyman *et al.* and Pollack *et al.* did not look at polypeptide levels. (Page 7 of the instant Office Action).

Applicants respectfully submit that the Hyman *et al.,* and Pollack *et al.* references, as stated in Applicants' previous Responses, teach that in general, gene amplification increases mRNA expression. Applicants further submit that Dr. Polakis' Declarations and Dr. Scott's Declaration were presented to support the position that there is a correlation between mRNA levels and polypeptide levels. Thus, taken together, all of the submitted evidence supports Applicants' position that gene amplification is more likely than not predictive of increased mRNA and polypeptide levels.

The Examiner further asserts that "Applicants have also previously acknowledged that 'the correlation between mRNA and protein level is not exact' ... and therefore, cannot be 'more likely than not true' by definition." (Page 7 of the instant Office Action).

Applicants respectfully submit that the Examiner appears to have misinterpreted Applicants' previous statement. Applicants have acknowledged only that protein levels cannot be "accurately predicted" from mRNA levels in the sense that the exact numerical amounts of protein present in a tissue cannot be determined based upon mRNA levels. Applicants respectfully submit, however, that the PTO's emphasis on the need to "accurately predict" protein levels based on mRNA levels misses the point. The asserted utility for the recited polypeptides and the claimed antibodies that bind them is in the diagnosis of cancer. What is relevant to use as a cancer diagnostic is relative levels of gene or protein expression, not absolute values, that is, that the gene or protein is differentially expressed in tumors as compared to normal tissues. Applicants need only show that there is a correlation between mRNA and protein levels, such that mRNA overexpression generally predict protein overexpression. A showing that mRNA levels can be used to "accurately predict" the precise levels of protein expression is not required.

Based on the above arguments, Applicants have clearly demonstrated a credible, specific and substantial asserted utility for the claimed PRO1788 polypeptide, for example, as diagnostic markers for colon tumors. Further, based on this utility and the disclosure in the specification, one skilled in the art at the time the application was filed would know how to use the claimed polypeptides.

Applicants therefore respectfully request withdrawal of the rejections of Claims 28-35 and 38-40 under 35 U.S.C. §101 and §112, first paragraph.

II. Claim Rejections Under 35 U.S.C. § 112, First Paragraph (Written Description)

Claims 28-33 and 39-40 remain rejected under 35 U.S.C. 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the

application was filed, had possession of the claimed invention. (Page 8 of the instant Office Action).

Applicants respectfully maintain the position that that Claims 28-33, 39 and 40 satisfy the written description requirement under 35 U.S.C. §112, first paragraph, for the reasons previously set forth in Applicants' previously filed Responses and Appeal Brief..

Applicants therefore respectfully request the Examiner to reconsider and withdraw the written description rejection of Claims 28-33, 39 and 40 under 35 U.S.C. §112, first paragraph.

CONCLUSION

In conclusion, the present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited. Should there be any further issues outstanding, the Examiner is invited to contact the undersigned agent at the telephone number shown below.

Although no fees are due, the Commissioner is hereby authorized to charge any fees, including any fees for extension of time, or credit overpayment to Deposit Account No. **08-1641**, referencing Attorney's Docket No. **39780-2830 P1C42**.

Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

Date: July 25, 2007

By:_____
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